

ORIGINAL ARTICLE

Metabolic syndrome, left ventricular hypertrophy and carotid atherosclerosis in hypertension: A gender-based studyCESARE CUSPIDI^{1,2}, CARLA SALA³, LAURA LONATI², FRANCESCA NEGRI², MARTA RESCALDANI³, ANNALISA RE², STEFANO MEANI⁴ & GIUSEPPE MANCIA^{1,2}¹Department of Health Science, University of Milano-Bicocca, Milano, Italy, ²Istituto Auxologico Italiano, Milano, Italy, ³Department of Clinical Sciences and Community Health, University of Milano, Fondazione Policlinico di Milano, Italy, and ⁴Divisione di Cardiologia, Ospedale di Rho, Italy**Abstract**

Background. The influence of gender on the association between metabolic syndrome (MS) and subclinical organ damage (OD) has been poorly investigated. The aim of this study was to investigate whether the risk of developing left ventricular hypertrophy (LVH) and carotid atherosclerosis is different in men and women with MS. **Methods.** A total of 3752 untreated and treated hypertensive patients (mean age 53.3 ± 12.6 , 52.7% men) were considered for this analysis. All patients underwent standard ultrasonographic investigations searching for LVH and carotid atherosclerosis. The MS was defined according to ATP III criteria. **Results.** LVH was more prevalent in women and men with the MS compared with their counterparts (58% vs 34% and 48% vs 33%, respectively, $p < 0.001$). This was also the case for carotid plaque prevalence (61% vs 42% and 57% vs 44%, $p < 0.001$). The prevalence of OD was not different between men and women with MS, after adjusting for confounders. In multivariate analysis, abdominal obesity was the most important MS component independently related to LVH in both genders, followed by blood pressure. As for carotid plaques, blood pressure, hyperglycemia and hypertriglyceridemia turned out to be independent correlates regardless of gender. **Conclusions.** Our data indicate that MS is associated with a higher risk of LVH and carotid atherosclerosis irrespective of gender; these findings do not support a gender influence in the association between MS and subclinical OD.

Key Words: Gender, metabolic syndrome, organ damage**Introduction**

The metabolic syndrome (MS) is a clinical entity characterized by the coexistence of multiple risk factors for cardiovascular disease (CVD) and diabetes mellitus (1,2), such as raised blood pressure (BP), hyperglycemia, elevated triglyceride levels, low high-density cholesterol levels and central obesity. The pathogenesis of MS is incompletely defined; increasing evidence indicates that both insulin resistance and activation of the renin–angiotensin–aldosterone system play a central role in this syndrome, which is associated with an adverse cardiovascular (CV) prognosis (3,4). Individuals with MS have a two- to three-fold higher risk of developing CVD within 10 years than their counterparts (2); the increased CV risk may be related to the development of more pronounced subclinical alterations in cardiac and vascular structures in subjects with MS.

Echocardiographic studies in population-based samples or hypertensive cohorts have consistently shown that subjects with metabolic risk factors or with MS have increased left ventricular mass (LVM), higher prevalence of left ventricular hypertrophy (LVH) and diastolic dysfunction compared with their counterparts without MS (5–8). Over the past decade, the impact of MS on large arterial vessels (i.e. carotid wall) has been analyzed by ultrasonographic studies either in hypertensive subjects as in the general population. In most of these studies, both carotid intima-media thickness (IMT) and plaque prevalence were found to be higher in subjects with MS and were significantly related with the number of MS components (9–11). Despite a large body of data on the relationship of MS with cardiac and extra-cardiac organ damage (OD), only few studies focused on gender-related differences in such an

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association and their results provided non-univocal information (12–16). Thus, the aim of the present study in a large cohort of subjects with essential hypertension was to investigate whether the likelihood of having LVH and carotid atherosclerosis is different between men and women with MS.

Methods

Study population

The analysis was performed on data from the Evaluation of Target Organ Damage in Hypertension (ETODH) study, a cross-sectional observational registry providing detailed information on hypertension-related OD in untreated and treated subjects with uncomplicated essential hypertension. Details of the study protocol have been previously reported (12). Entry criteria included the absence of previous clinically overt CV disease, secondary causes of hypertension and life-threatening conditions. After their informed consent had been obtained during the initial visit, all patients underwent the following procedures, which were completed within 1–4 weeks: medical history and physical examination, clinic BP measurement, blood and urine sampling, standard 12-lead electrocardiogram, non-mydriatic retinography, cardiac, renal and carotid ultrasonography. The study protocol was approved by the Ethics Committee of one of the institutions involved.

Blood pressure measurement

Clinic BP was measured at two different visits in the outpatient clinic using a mercury sphygmomanometer and taking the first and fifth phases of Korotkoff sounds to identify systolic (SBP) and diastolic BP (DBP), respectively. Measurements started after the subjects had rested for 5 min in the sitting position. Three measurements were taken at 1-min interval in each occasion and the average of six values was used to define clinic SBP and DBP.

Echocardiography

Echocardiographic examinations were carried out according to standardized procedures. M-mode, two-dimensional, Doppler examinations were made with commercially available instruments. LVM was estimated from end-diastolic left ventricular internal diameter (LVIDd), interventricular septum (IVST) and posterior wall thickness (PWT) according to the Devereux's formula (17) and normalized to BSA and height^{2.7} to obtain LVM indexes (LVMI). Relative wall thickness (RWT) was calculated as $(2 \times \text{PWT}) / \text{LVIDd}$; left ventricular (LV) filling was assessed by mitral flow with standard pulsed Doppler technique, the following parameters were considered:

early diastolic peak flow velocity (E), late diastolic peak flow velocity (A) and their ratio (E/A).

Carotid ultrasonography

Images of extra-cranial carotid walls (common, bifurcation and internal carotid arteries) were obtained in several projections by high resolution, linear array 7.5–10.0-MHz probes. Plaques were sought in the near and far walls of the entire extra-cranial tree, and intima-media thickness (IMT) was measured in the posterior wall of both common carotid arteries 5, 10, 15, 20 and 25 mm caudally to the bifurcation (18). For statistical purposes, all 10 measurements were averaged to obtain the mean value of common carotid IMT. Details about reproducibility of LVM and IMT measurements in our laboratory have been previously reported (19).

Definition of organ damage

OD was defined by the presence of ultrasonographic LVH and vascular alterations. In particular, LVH was defined as LVMI equal to or higher than 51 g/m^{2.7} in men and 47 g/m^{2.7} in women (20,21). The presence of at least one carotid atherosclerotic plaque or diffuse intima-media (IM) thickening was taken as evidence of vascular alterations.

A plaque was defined as a focal thickening greater than 1.3 mm in any segment of carotid arteries (22). Diffuse IM thickening was diagnosed when the average common carotid wall thickness exceeded 0.9 mm (23).

Definition of the metabolic syndrome

MS was diagnosed when three or more of the following criteria were present: abdominal obesity (waist circumference >102 cm in men and >88 cm in women), hypertriglyceridemia (>150 mg/dl or 1.69 mmol/l or drug treatment for elevated triglycerides), reduced high-density lipoprotein (HDL) cholesterol (<40 mg/dl or 1.04 mmol/l in men and <50 mg or 1.29 mmol/l in women) or drug treatment for reduced HDL-cholesterol, high BP (SBP \geq 130 mmHg or DBP \geq 85 mmHg or drug treatment for hypertension) and high fasting blood glucose (\geq 100 mg/dl or \geq 6.1 mmol/l) or drug treatment for elevated glucose (1,2).

Statistical analysis

Statistical analysis was performed by the SAS system (version 6.12; SAS Institute Inc., Cary, North Carolina, USA). Values were expressed as means \pm SD or as percentages. Continuous variables were compared by analysis of variance (ANOVA), using the Student's *t*-test for dual comparisons. Analysis of categorical data was carried out by the χ^2 test or Fischer's exact

test when appropriate. To investigate the association between individual components of MS and markers of OD such as LVH and carotid plaques, multiple logistic regression analyses were performed in both genders by calculating odd ratios and their 95% confidence limits. For all analyses, a $p < 0.05$ was considered statistically significant.

Results

The ETODH registry started in January 1999 and by the end of July 2006 had enrolled 3752 subjects (52.7% men) with untreated (29.5%) or treated essential hypertension. Mean age was 53.3 ± 12.6 (range 18–90) years. Mean SBP and DBP were 146 ± 18 and 92 ± 10.0 mmHg, respectively; 22.2% of the study sample were smokers, 5.2% had type 2 diabetes mellitus and 40.9% had the MS. Men were younger than women, had higher DBP, body mass index, fasting blood glucose, triglyceride and uric acid, but lower SBP, heart rate, total and HDL-cholesterol values. The prevalence of LVH tended to be higher in women (43.0% vs 39.0%) whereas that of carotid plaques showed an opposite trend (48.9% vs 50.0), respectively, without achieving statistical significance in both cases ($p = 0.06$ and $p = 0.50$).

In men, the most common component of the MS (other than high BP) was high fasting blood glucose (43.1%), followed by low HDL-cholesterol (40.5%), hypertriglyceridemia (35.7%) and abdominal obesity (25.8%). In women, low HDL-cholesterol (39.4%) was the most frequent feature of the MS followed by abdominal obesity (35.5%), hypertriglyceridemia (24.9%) and high fasting blood glucose (28.1%).

For the present analysis, patients were divided in four groups according to the gender and the presence of MS. Table I shows that both men and women with MS were older, were more frequently treated with antihypertensive drugs, had higher SBP and uric acid values, and showed increased

prevalence of type 2 diabetes mellitus than their gender counterparts, the differences being in all instances statistically significant.

As reported in Table II, prevalence of LVH was approximately 40% higher in men and 70% higher in women with MS compared with their gender counterparts ($p < 0.01$ for both). A similar trend was observed for carotid IMT and carotid plaque, this latter alteration being 30% and 45% more frequent in men and women with MS, respectively, compared with their gender counterparts ($p < 0.01$ for both). Of note, the prevalence of LVH and carotid plaque was not different between men and women with MS, after adjusting for age, clinic BP and anti-hypertensive treatment.

In order to analyze the factors involved in the pathogenesis of OD, the relation of LVH and carotid plaque with abdominal obesity, hyperglycemia, hypertriglyceridemia, low HDL-cholesterol, above median values of clinic SBP and age was analyzed by a logistic regression model in both genders. As shown in Figure 1, in men, the strongest independent correlate of LVH was abdominal obesity, followed by age, SBP and fasting blood glucose; neither HDL-cholesterol nor triglyceride were related with this cardiac phenotype. In women, abdominal obesity, age and SBP but not fasting blood glucose were independently correlated with LVH. In both genders, age, SBP, fasting blood glucose and triglycerides were independently associated with carotid plaque.

Finally, prevalence rates of LVH and carotid plaque were significantly higher in patients with MS regardless of the absence (35%, 42%, vs 27%, 31%, p at least < 0.05) or the presence of antihypertensive treatment (59%, 62%, vs 38%, 51%, p at least < 0.001).

Discussion

This cross-sectional study compared the extent of subclinical cardiac and vascular OD in a large sample

Table I. Clinical characteristics of the study population divided by gender and the presence of metabolic syndrome (MS).

	Men MS–	Men MS+	Women MS–	Women MS+	p-value	
					Men ^a	Women ^b
Age (years)	51.2 ± 13.2	52.8 ± 11.5	53.3 ± 12.8	57.4 ± 11.7	0.005	< 0.0001
Clinic SBP (mmHg)	144.6 ± 16.7	146.5 ± 17.4	145.9 ± 17.5	149.5 ± 19.7	0.02	< 0.0001
Clinic DBP (mmHg)	93.4 ± 9.4	94.2 ± 10.3	91.0 ± 9.6	91.0 ± 9.8	0.08	0.98
Clinic heart rate (beats/min)	71.5 ± 11.7	71.9 ± 12.1	73.2 ± 11.9	73.2 ± 12.1	0.46	0.94
Body mass index (kg/m ²)	25.4 ± 2.7	28.8 ± 3.8	23.5 ± 3.6	28.8 ± 4.6	< 0.0001	< 0.0001
FBG (mg/dl)	94.9 ± 14.8	111.4 ± 30.5	89.0 ± 9.6	108.1 ± 29.8	< 0.0001	< 0.0001
Total cholesterol (mg/dl)	210.5 ± 37.5	220.4 ± 58.2	222.6 ± 38.9	231.0 ± 45.7	< 0.0001	< 0.0001
HDL-cholesterol (mg/dl)	49.1 ± 12.6	37.5 ± 10.6	58.9 ± 15.5	45.5 ± 12.6	< 0.0001	< 0.0001
Triglycerides (mg/dl)	108.0 ± 52.6	191.4 ± 116.8	92.5 ± 38.7	158.1 ± 93.2	< 0.0001	< 0.0001
Uric acid (mg/dl)	5.7 ± 1.8	6.1 ± 1.9	4.2 ± 1.8	5.0 ± 1.4	< 0.0001	< 0.0001
Current smoking (%)	23.5	27.2	18.3	20.2	0.13	0.07
Diabetes mellitus (%)	2.1	10.7	0.4	11.7	< 0.0001	< 0.0001
AHT (%)	64.5	72.8	67.0	83.3	0.03	0.002

Data are shown as means ± SD or percent. ^ap-value: men MS– vs men MS+; ^bp-value: women MS– vs women MS+. SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL, high-density lipoprotein; AHT, anti-hypertensive treatment.

Table II. Ultrasonographic findings in the study population as a whole and divided by gender.

	Men MS-	Men MS+	Women MS-	Women MS+	p-value	
					Men ^a	Women ^b
LVIDd (mm)	49.3 ± 4.0	50.0 ± 4.0	45.3 ± 3.5	46.5 ± 4.1	<0.0001	<0.0001
LVIDs (mm)	29.6 ± 4.0	30.2 ± 4.5	26.5 ± 3.8	27.3 ± 4.1	0.0005	<0.0001
IVSTd (mm)	10.6 ± 1.3	11.1 ± 1.4	9.5 ± 1.1	10.2 ± 1.3	<0.0001	<0.0001
PWTd (mm)	9.6 ± 1.0	10.0 ± 1.0	8.7 ± 0.9	9.3 ± 1.0	<0.0001	<0.0001
RWT	0.41 ± 0.05	0.43 ± 0.05	0.40 ± 0.05	0.42 ± 0.06	<0.0001	<0.0001
LA diameter (mm)	37.1 ± 4.4	39.2 ± 4.5	33.9 ± 4.4	36.7 ± 4.5	<0.0001	<0.0001
E/A ratio	1.10 ± 0.38	1.10 ± 1.01	1.11 ± 0.38	0.97 ± 0.36	0.80	<0.0001
LVM (g)	213.1 ± 47.8	234.4 ± 55.1	159.3 ± 38.5	183.4 ± 44.9	<0.0001	<0.0001
LVM/BSA (g/m ²)	111.1 ± 24.1	116.5 ± 24.7	96.8 ± 21.3	102.9 ± 22.6	<0.0001	<0.0001
LVM/h ^{2.7} (g/h ^{2.7})	47.5 ± 11.1	52.8 ± 12.5	43.7 ± 10.8	50.8 ± 12.5	<0.0001	<0.0001
LVH (%)	33.0	48.0	34.1	58.6	0.0003	0.0002
Carotid IMT (μm)	695 ± 153	737 ± 156	671 ± 141	735 ± 179	<0.0001	<0.0001
Carotid plaque (%)	44.5	56.8	41.8	61.0	<0.0001	<0.0001

Data are shown as means ± SD or percent. ^ap-value: men MS- vs men MS+; ^bp-value: women MS- vs women MS+. MS, metabolic syndrome; LVIDd, left ventricular internal diameter diastole; LVIDs, left ventricular internal diameter systole; IVSTd, interventricular septum thickness diastole; PWTd, posterior wall thickness diastole; RWT, relative wall thickness; LA, left atrium; E, early diastolic mitral flow; A, late diastolic mitral flow; LVM, left ventricular mass; BSA, body surface area; h, height; LVH, left ventricular hypertrophy; IMT, intima-media thickness.

of untreated and treated hypertensive subjects categorized according to the MS defined by the Adult Treatment Panel III and gender. This study clearly indicates that MS is associated with a greater risk of LVH and carotid atherosclerosis both in men and women; our data, however, do not support a gender difference in the association between MS and subclinical cardiac and carotid OD. This conclusion is strengthened by the observation that: (i) LVMI, carotid IMT as well as LVH and carotid plaque prevalence were significantly higher in patients with MS compared with their non-MS counterparts irrespective of gender; (ii) the extent

of cardiac and extra-cardiac OD was similar in men and women with MS after adjusting for confounders; (iii) in multivariate analyses abdominal obesity, age and SBP were the best independent correlates of LVH both in men and women; this was also the case for carotid plaque, being age and SBP the major determinants of this ultrasonographic phenotype in both genders. Thus, our data provide a new piece of information on the controversial interaction between sex and OD in the MS by showing that the correlates and extent of cardiac and extra-cardiac damage in patients with MS are not different between men and women.

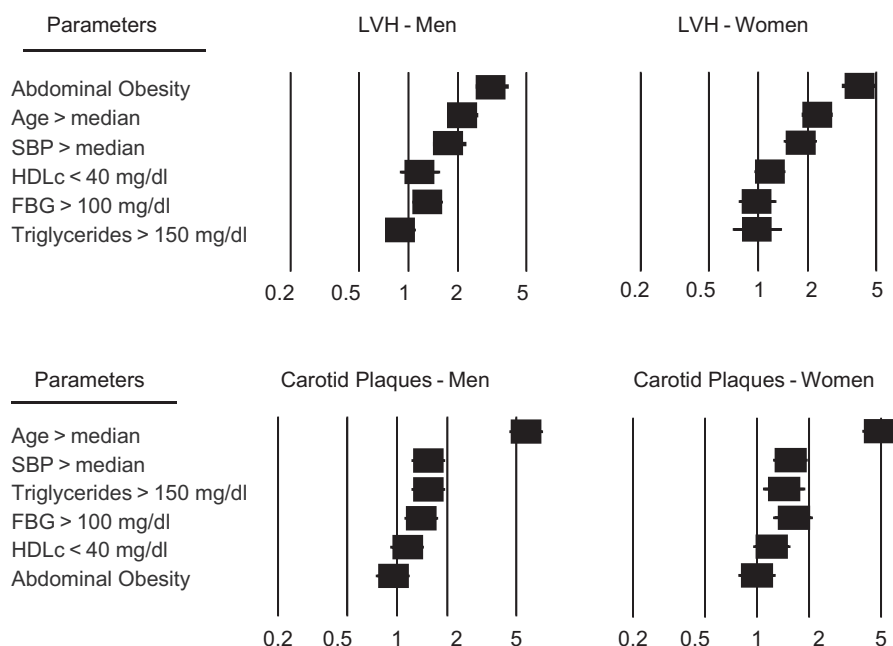


Figure 1. Forrest plots showing odds ratios and 95% confidence intervals (CI) of independent variables associated with left ventricular hypertrophy (LVH, upper panel) and carotid plaques (lower panel) in hypertensive men and women. SBP, systolic blood pressure; FBG, fasting blood glucose.

Our results are not in keeping with previous reports indicating that the effects of MS on LV structure and early carotid atherosclerosis are prevalent in women. Among 618 non-diabetic, untreated hypertensive subjects, a greater prevalence of LVH was found by Schillaci et al. (13) in women with MS compared with those without the syndrome (37% vs 14%, $p < 0.001$); such a difference was not present in men (39% vs 29%, $p < 0.09$). In a population-based survey of 1588 participants in the Salzburg Atherosclerosis Prevention program at High Individual Risk (SAPHIR) study, Iglseder et al. (14) reported that the extent of carotid plaque and IMT were greater in subjects with MS; after adjusting for established risk factors, however, the difference in carotid plaque score remained significant only in women. The higher prevalence of MS in our study sample (41%) compared with the above-mentioned studies (27% and 16%, respectively) may partly explain this discrepancy. Thus, our results do not support the view that MS is a condition at less risk for subclinical OD in men than in women. Our conclusion is in agreement with the findings provided by two European population-based studies. In the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study, MS was associated with increased LV mass index in the whole sample (97.4 ± 23.8 vs 83.6 ± 19.9 g/m²), as well as in men and women without differences between genders, in younger and older subjects (24); the differences remained significant after adjustment for age, gender, smoking, alcohol consumption, 24-h average SBP and history of CV events. Among 2228 individuals (2036 men and 2192 women) living in Stockholm County, Sweden (16), the prevalence of LVH was 12.8% in men with the MS and 7.9% in men without the syndrome ($p = 0.0003$); the corresponding figures in women were 9.9% and 3.3%, respectively ($p < 0.0001$). In men, hypertension was the only component significantly associated with LVH after adjustments (OR = 3.40; 95% CI = 1.99–5.82); in women, waist circumference (OR = 1.63; 95% CI 1.03–2.57) and glycemia (OR = 1.77; 95% CI 1.13–2.79) were also independently associated with LVH, after hypertension (OR = 4.41; 95% CI 2.50–7.76). Sex-specific relations between LV mass, left atrial size and glucose metabolism, estimated by the homeostasis model assessment, have been investigated in a pioneering study in the Framingham population (25), showing that a relation between insulin resistance and LV mass was present only in women; additional adjustments for BMI, however, rendered this gender-related difference non-significant.

Several mechanisms may explain the interaction of the MS with cardiac and vascular structures. Available evidence indicates that BP plays a pivotal role in the development of preclinical OD and that the impact of BP on the heart and vessels may be amplified by metabolic factors. The adverse cardiac effects of MS have

been mostly related to high-normal or frankly elevated BP values and to central obesity, namely to a combination of pressure and volume overload (26). Recently Guerra et al. demonstrated in 380 overweight/obese hypertensives that the effects of the MS on LV parameters are mainly driven by the degree of adiposity (27). Metabolic components, such as hyperglycemia and dyslipidemia, probably contribute to the abnormal loading conditions by decreasing large artery compliance; hyperinsulinemia may also stimulate the growth of myocardial cells. Finally, the role of cytokines produced by the abdominal adipose tissue should be considered in the pathogenesis of LVH and vascular damage over and beyond hemodynamic factors.

The main finding of the present study is that among the MS components abdominal obesity and BP were the most important correlates of LVH without significant sex-related differences. In a clinical perspective, this observation suggests that obese hypertensive men and women should be screened for LVH by echocardiography and that prevention/treatment of obesity should reduce the likelihood of new-onset and persistent LVH.

Our data also point toward a synergic effect of raised BP levels and metabolic alterations such as hyperglycemia and hypertriglyceridemia in determining carotid atherosclerosis in either men and women. Thus carotid subclinical alterations should be systematically searched in hypertensive patients with concomitant metabolic risk factors, regardless the gender in order to optimize the clinical management.

Study limitations

Our study sample included only Caucasian subjects and hypertensive patients referred to a specialist centre; thus, our results should not be extended to different ethnic groups or to the general population. The inclusion of patients on antihypertensive treatment probably affected the relationship between MS and OD, as treatment-related BP decrease might have reduced the prevalence and degree of OD in our study. We found, however, that cardiac and extra-cardiac OD was significantly greater in patients with MS independently of the antihypertensive drugs; in particular, the difference in organ involvement was even more pronounced in treated than in untreated individuals. Lastly, our cross-sectional analysis does not permit any causal inference.

Conflict of interest: The authors declare no conflict of interest. The authors alone are responsible for the content and the writing of the paper.

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